Engineering HIV-1-resistant T-cells from short-hairpin RNA-expressing hematopoietic stem/progenitor cells in humanized BLT mice.

Journal: PLoS One

Publication Year: 2012

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PubMed link: 23300932

Funding Grants: CSUN-UCLA Bridges to Stem Cell Research

Public Summary:
New vector therapy for using human hematopoietic stem/progenitor cell (HSPC) to transplant HIV-resistant bone marrow to build an immune system able to fight HIV infection is described in this study.

Scientific Abstract:
Down-regulation of the HIV-1 coreceptor CCR5 holds significant potential for long-term protection against HIV-1 in patients. Using the humanized bone marrow/liver/thymus (hu-BLT) mouse model which allows investigation of human hematopoietic stem/progenitor cell (HSPC) transplant and immune system reconstitution as well as HIV-1 infection, we previously demonstrated stable inhibition of CCR5 expression in systemic lymphoid tissues via transplantation of HSPCs genetically modified by lentiviral vector transduction to express short hairpin RNA (shRNA). However, CCR5 down-regulation will not be effective against existing CXCR4-tropic HIV-1 and emergence of resistant viral strains. As such, combination approaches targeting additional steps in the virus lifecycle are required. We screened a panel of previously published shRNAs targeting highly conserved regions and identified a potent shRNA targeting the R-region of the HIV-1 long terminal repeat (LTR). Here, we report that human CD4(+) T-cells derived from transplanted HSPC engineered to co-express shRNAs targeting CCR5 and HIV-1 LTR are resistant to CCR5- and CXCR4- tropic HIV-1-mediated depletion in vivo. Transduction with the combination vector suppressed CXCR4- and CCR5- tropic viral replication in cell lines and peripheral blood mononuclear cells in vitro. No obvious cytotoxicity or interferon response was observed. Transplantation of combination vector-transduced HSPC into hu-BLT mice resulted in efficient engraftment and subsequent stable gene marking and CCR5 down-regulation in human CD4(+) T-cells within peripheral blood and systemic lymphoid tissues, including gut-associated lymphoid tissue, a major site of robust viral replication, for over twelve weeks. CXCR4- and CCR5- tropic HIV-1 infection was effectively inhibited in hu-BLT mouse spleen-derived human CD4(+) T-cells ex vivo. Furthermore, levels of gene-marked CD4(+) T-cells in peripheral blood increased despite systemic infection with either CXCR4- or CCR5- tropic HIV-1 in vivo. These results demonstrate that transplantation of HSPCs engineered with our combination shRNA vector may be a potential therapy against HIV disease.